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TOBACCO INDUSTRY RESEARCH COMMITTEE
150 EAST FORTY SECOND STREET NEW YORK 17, N. Y.

RENEWAL
Application For Research Grant

#9282

July 1, 1957 - June 30, 1958

Date: April 11, 1957

1. Name of Investigator: Janet Travell, M.D.

2. Title: Associate Professor of Clinical Pharmacology.

3. Institution & Address: Cornell University Medical College,
1300 York Avenue
New York 21, New York

4. Project or Subject: Cardiac Effects of Nicotine in the Rabbit with Experimental Coronary Atherosclerosis.

5. Detailed Plan of Procedure (Use reverse side if additional space is needed):

Briefly to summarize our definitive results to date:

In cholesterol-fed male rabbits, we have observed the development of occlusive coronary atherosclerosis usually in from 4 to 6 months, as shown by the appearance of ergonovine-induced electrocardiographic changes in serial tests and by final pathologic study of the heart. Every animal with a positive ergonovine test has shown coronary atherosclerosis at postmortem.

One-eighth of 16 ergonovine-positive rabbits, similarly tested with intravenous nicotine bitartrate, have shown acute electrocardiographic changes suggestive of constriction of the coronary arteries (S-T segment depression). No such changes were observed in 12 normal rabbits.

Perfusion of the coronary arteries of the isolated heart has been carried out on 16 atherosclerotic hearts of ergonovine-positive rabbits and on 14 normal rabbits. Data on the effects of nicotine in these experiments relate to coronary flow, amplitude of contraction and heart rate.

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The results (Travell, J., Karp, D. and Rinzler, S. H.: Nicotine Effects on Normal and Atherosclerotic Hearts, Federation Proc., p. 341, 1957) show that the immediate effect of nicotine is consistently a decrease in coronary flow. On the average, the degree of vaso-constriction for the larger doses used (0.05-0.1 mg.) appears to be greater for the normal than for the atherosclerotic heart; in no instance did an atherosclerotic heart show significant coronary vasodilation after nicotine. That the atherosclerotic coronary system can dilate at this time is shown by its vasodilator response to nitroglycerin. Effects of nicotine on heart rate and amplitude of contraction were qualitatively similar in normal and atherosclerotic hearts.

In the atherosclerotic isolated heart, nicotine appears to be a less potent coronary constricting agent than either ergonovine or xxxx vasopressin. Preliminary experiments indicate that the effects of nor-epinephrine in the isolated heart are similar to those of nicotine.

Our chief objectives next year will be to:

1) Determine the stage of coronary atherosclerosis at which a change occurs in the reactivity of the coronary tree to ergonovine and nicotine.

For this, we will perfuse the heart of the ergonovine-negative cholesterol-fed rabbit, and relate the results to the pathologic changes seen in the coronary arteries after perfusion. At the termination of perfusion, on section of the heart satisfactory pathologic detail is obtained with respect to early intimal lipid deposits, later foam cells and plaques, and finally deterioration of the elastic membrane beneath the plaques. Pathologic definition of the myocardium is poor after perfusion.

2) Shorten the time required to produce experimental coronary atherosclerosis in the cholesterol-fed rabbit.

Measures will be tried such as anti-thyroid drugs (effective in the dog), cold stress (effective in the rat), or hormone administration. A larger supply of atherosclerotic hearts is needed for direct study in the perfusion apparatus and possibly also for the papillary muscle preparation. The latter would represent a new step in the pharmacology of the atherosclerotic heart.

3) Increase the sensitivity of the ergonovine test so as to detect coronary atherosclerosis earlier in its course.

Possibly this may be accomplished by modification of dosage, combination with some other vasoconstrictor drug, or by substituting another vasoconstrictor agent for ergonovine.

4) Elucidate mechanisms of action of nicotine and other agents on the atherosclerotic as compared with the normal heart.

The influence of autonomic blocking agents on the response to nicotine in normal and atherosclerotic hearts will be investigated.

Comparisons of the effects of some coronary dilator agents may also be informative.

5) Extend the electrocardiographic study of nicotine effects to the isolated heart.

In view of the low incidence of acute electrocardiographic changes after nicotine (0% in normal, 12.5% in atherosclerotic rabbits), it does not seem worthwhile at the moment to accumulate further data on the electrocardiographic effects of nicotine in the intact animal.

We propose to extend this phase of the work to include electrograms of the isolated heart during perfusion.

The addendum presents in tabular and chart form some of the data derived from this investigation.

6. Budget Plan:

Part-time research associate
(S.H. Rinzler, M.D.)
Full-time research assistant, Ph.D.
Part-time laboratory man

Salaries		$9,100.
Expendable Supplies		3,000.
Permanent Equipment	Sanborn Viscoscope, Model 169 A with booster amplifier	570.
Overhead	(15%)	1,470.
Other	Pathology, photography	1,393.
	5% retirement, 2% social security	637.
Total		16,170.00 TOTAL

7. Anticipated Duration of Work:

Two years

8. Facilities and Staff Available:

The usual facilities of the Department of Pharmacology.
Dr. Dorothy Karp will be replaced by a new Ph.D. assistant.
Dr. Seymour H. Rinzler will next year be on our payroll.

9. Additional Requirements:

July 1, 1958 - June 30, 1959
$15,000. / overhead

10. Additional Information (Including relation of work to other projects and other sources of supply):

The grant from the National Heart Institute, National Institutes of Health, Public Health Service, for studies on cardiovascular pain will expire this year, on September 30, 1957.

Signature
Director of Project
S/ Janet Travell

Business Office of the Institution
/S/ E. W. Taylor

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INITIAL STATE OF ISOLATED PERFUSED HEART OF RABBIT

Heart	Total Number	Coronary Flow	Heart Rate	Amplitude of Contraction
		ml./min.	beats/min.	mm.
Normal	32	15.7 (9-23)*	151 (98-200)	33.0 (7-79)
Athero-sclerotic	29	19.5 (8 - 32)	126 (36-196)	26.9 (6-52)
	t-test	$p < 0.01$	$p < 0.01$	$p < 0.001$

*Figures in parentheses indicate range.